TO D. Zuhs, PhD

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
(Case No. 142/003/PCT; 03-766)

PATENT

In re Application of: Light et al.	
Serial No.: 09/582,492	**Before the Examiner:** J. Switzer
Filed: March 6, 2002	**Group Art Unit:** 1634
For: Detection of Human Papilloma Virus in Papanicolaou (Pap) Smears	

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION PURSUANT TO 37 C.F.R. § 1.132

I, Gerard J. Nuovo, hereby declare:

1. I am a Professor of Pathology at the Ohio State University Medical Center. I am also a named co-inventor on the above-described patent application. I have an M.D. from the University of Vermont Medical College and have been engaged in research on gynecologic pathology, focusing on cervical diseases, and infectious disease detection, focusing on HPV and *in situ*-based methodologies, for eighteen years. My *curriculum vitae* is attached hereto as Appendix A.

2. I authored an article entitled "Detection of Human Papillomavirus in Papanicolaou Smears: Correlation With Pathologic Findings and Clinical Outcome," which was published in Diagnostic Molecular Pathology in June of 1998 (Nuovo, 1998; *Diagn. Mol. Pathol.* 7:158-63).

3. My 1998 reference discloses the use of Oncor's high-risk HPV consensus probe to detect different oncogenic HPV types in cervical biopsies by *in situ* hybridization under low stringency conditions (p. 159, 161). In particular, my 1998 reference discloses that the Oncor high-risk consensus probe can be used under low stringency conditions to detect the oncogenic HPV types 16, 18, 30, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, and 70, but not the HPV types 6, 11, 42, 43, and 44 (p. 161). My 1998 reference also discloses that Oncor's high-risk HPV consensus probe contains multiple high-risk HPV types (p. 160).

4. My 1998 reference does not disclose the specific composition of the Oncor high-risk HPV consensus probe (*i.e.*, the particular HPV types comprising the consensus probe or proportions of these particular HPV types).

5. Accompanying this Declaration is a copy of my notes from before June of 1998 (Exhibit A) documenting that a high-risk HPV consensus probe comprising 200 ng/ml or 500 ng/ml of HPV type 16 DNA would detectably hybridize to HPV types 6/11 under conditions of low stringency.

6. Using the teachings of my 1998 reference and knowledge in the art at the time my 1998 reference was published, a person of ordinary skill in the art would not be able to determine the particular HPV types or proportions of the particular HPV types comprising the Oncor high-risk HPV consensus probe, and as a result, would not be able to prepare a high-risk HPV consensus probe that does not detectably hybridize to the genomic sequence of a low-risk HPV type.

7. I co-authored an article entitled "A Comparison of Subgenomic and Genomic DNA Probes for Detection and Typing of Human Papillomavirus by in situ Hybridization," which was published in the Journal of Histotechnology in June of 1995 (Nuovo *et al.*, 1995, *J. Histotech.* 18:105-10).

8. My 1995 reference discloses the use of eight different high-risk HPV consensus probes, including high-risk HPV consensus probes obtained from both Digene Diagnostics and ONCOR that contain probes generated from specific subgenomic areas of (i) HPV types 16 and 18 or (ii) HPV types 31, 33, and 35 (page 106).

9. My 1995 reference does not disclose the specific proportions of the probes in the Digene Diagnostics or ONCOR high-risk HPV consensus probes.

10. Using the teachings of my 1995 reference and knowledge in the art at the time my 1995 reference was published, a person of ordinary skill in the art would not be able to determine the proportions of the probes in the Digene Diagnostics or ONCOR high-risk HPV consensus probes, and as a result, would not be able to prepare a high-risk consensus probe that does not detectably hybridize to the genomic sequence of a low-risk HPV type.

11. At the time my 1995 reference was published, a person of ordinary skill in the art would not have appreciated (and, in fact, the named inventors of the above-described application did not yet appreciate) that a high-risk HPV consensus probe that did not detectably hybridize to the

genomic sequence of a low-risk HPV type under low stringency conditions could be prepared by decreasing the proportions of certain probes in the high-risk HPV consensus probe.

12. I have reviewed the article entitled "Human papillomavirus testing by hybrid capture appears to be useful in triaging women with a cytologic diagnosis of atypical squamous cells of undetermined significance," which was published in the American Journal of Obstetrics and Gynecology in March of 1995 (Cox *et al.*, 1995, *Am. J. Obstet. Gynecol.* 172:946-54).

13. At the time the Cox *et al.*, 1995 reference was published, a person of ordinary skill in the art would have appreciated that hybrid capture high-risk HPV probe reagents such as the one disclosed by Cox *et al.* would detectably hybridize to the genomic sequence of a low-risk HPV type, and moreover, would generate false positives with respect to low-risk HPV types.

14. At the time the above-described application was filed, a person of ordinary skill in the art would have expected a high-risk HPV consensus probe to detectably hybridize to the genomic sequence of both low-risk and high-risk HPV types under low stringency conditions, and to not detectably hybridize to the genomic sequence of either low-risk HPV types or high-risk HPV types other than those used to generate the high-risk HPV consensus probe under high stringency conditions.

15. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed: _____
Gerard J. Nuovo

Dated: 9.18.06